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Applicants:	Andrew VAILLANT et al.
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For:	ANTIVIRAL OLIGONUCLEOTIDES
Art Unit:	1648
Examiner:	HURT, Sharon L.
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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Assistant Commissioner for Patents
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Sir:

Please find enclosed herewith form PTO/SB/33 for the pre-appeal brief request for review. Please consider the reasons below for which the review is being requested.

A Notice of Appeal is being filed concurrently.

REASONS:

The Applicants first submit that the Examiner has raised **new rejection matter** in the Advisory Action regarding claims 41-43 which were not rejected previously in the Final Official Action dated December 15, 2007. Thus, it is believed that the Examiner went beyond her mandate and issued new rejections which had never been submitted previously. Thus, the Examiner's rejection of claims 41-43 under 35 U.S.C. § 102(b) as being anticipated by Andreola *et al.* and under 35 U.S.C. §. 102(e) as being anticipated by Peyman *et al.* is improper. It is thus respectfully requested that it be withdrawn.

Claims 28-29 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Andreola *et al.* In this regard, the Applicants point out that claim 28 has been amended in the response dated February 9, 2007, to claim a method for the prophylaxis or treatment of viral infections caused by a virus of the family selected from the group consisting of herpesviridae, poxviridae, hepadnaviridae, arenaviridae, bunyaviridae, coronaviridae, filoviridae, flaviridae, orthomyxoviridae, paramyxoviridae, rhabdoviridae and togaviridae. Contrary to the subject matter claimed in the present application and as acknowledged by the Examiner, Andreola *et al.* **only teach** a specific sequence having high affinity to

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RNAse H domain of HIV-1 RT. Nowhere is it taught or even suggested in Andreola *et al.* that oligonucleotides may have an antiviral activity against other viruses.

In addition, the Applicants wish to point out that the Examiner, in her own arguments presented in the Final Office Action, suggests that Andreola *et al.* not only teaches that "*oligonucleotides have antiviral activity due to the sequence*", but also discloses that sequences that fold "*into a pseudoknot motif were found to bind HIV-1 RT with high affinity*". On page 1, second column, lines 7 and 8, it is clearly stated in Andreola *et al.* that *"sequences folding into the pseudoknot motif were found to bind HIV-1 RT with high affinity."* In the same paragraph in Andreola *et al.*, it is disclosed that the SELEX technique was used to isolate an RNA with a pseudoknot structure known as the "Tuerk-type pseudoknot". By definition, and as recognized by a person skilled in the art, a "pseudoknot motif" is an RNA secondary structure containing two stem-loop structures in which the first stem's loop forms part of the second stem. A classical pseudoknot is formed through a base pairing interaction between nucleotides in the loop of a stem loop and an adjacent single-stranded region. Consequently, in order to fold into a "pseudoknot", there is a need for specific nucleotides to be present in a stem loop and in an adjacent single-stranded region in order to allow pairing between the loop and the single-stranded region.

In regards to the "Tuerk-type pseudoknot", Andreola refers to the document of Tuerk *et al.* (1992; PNAS, 89: 6988-6992). A person skilled in the art, after analyzing the consensus pseudoknot motif known as the "Tuerk-type pseudoknot", would acknowledge that it is clearly a motif which is sequence dependent in order to fold properly and to bind HIV-1 RT. To the contrary, the Applicants respectfully point out that the oligonucleotides used in the present invention are not sequence dependent and can even be randomer oligonucleotides. It is disclosed at page 14 of the present description that the term "randomer" is intended to mean a single stranded DNA having a wobble (N) at every position, such as a NNNNNNNNNNN. In addition, at page 34 of the present description, it is clearly disclosed that for a randomer oligonucleotide of 40 bases in length, any particular sequence in the population would theoretically represent only $1/4^{40}$ or $8.27X10^{-25}$ of the total fraction. Given that 1 mole = $6.022X10^{23}$ molecules, and that the fact that the largest synthesis is currently done at 15 micromole scale, all possible sequences will not be present, and also, each sequence is present most probably as only one copy. Consequently, by its inherent properties, the oligonucleotides encompassed by claims 28, 29 and 41-43 are independent on the nature of the sequence, and thus not anticipated by the teaching found in Andreola *et al.*

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The Applicants also add that the SELEX method is a protocol that involves the selection from random pools of RNA and DNA molecules of oligonucleotides able to strongly bind to protein as ligands (see Andreola *et al.*, page 5032, first column, second paragraph). This method involves cycles of affinity selection by a protein from a heterogeneous population of DNA molecules, replication of bound species, *in vitro* transcription and reverse transcription to generate an enriched pool of bound DNA (Andreola *et al.*, page 5032, first and second column). Consequently, the SELEX method allows identifying only specific sequences that bind to the target protein. Andreola *et al.* never recognized that any oligonucleotide having any sequence and at least one phosphorothioate linkage had antiviral activity. In this regard, the Examiner specifically mentions in the Final Office Action that "*the SELEX approach was also used to identify high affinity DNA ligands against HIV-1 RT... Although they showed little structural similarity to the RNA aptamers, they were able to bind the RT... and inhibited specifically the DNA polymerase activity...*". This quote was taken from Andreola *et al.*, page 5032, right column, second paragraph, who references Schneider *et al.* (1995, Biochemistry, 34: 9599-9610). If one analyses the document of Schneider *et al.*, clearly the SELEX method allowed isolating specific sequences of DNA (30 in total) that bind the HIV-1 RT. For example, it is clearly demonstrated that the 30 specific molecules, which had unique sequences, could be classified into families according to common primary sequence elements (see Figure 2), and, for each family, a potential common secondary structure was generated (see Figure 3 in Schneider *et al.*).

Thus, since Andreola *et al.* **only** discloses sequence-specific oligonucleotides which are inhibitors of the HIV-1 RT, it is believed that claims 28, 29 and 41-43 are novel in view of the teaching of Andreola *et al.* and the Applicants respectfully submit that the 35 U.S.C. §102(b) rejection over Andreola *et al.* is improper, and requests that it be withdrawn.

The Examiner also maintains her rejection of claims 28 and 29 under 35 U.S.C. 102(e) as being anticipated by Peyman *et al.* In this regard, the Applicants resubmit that nowhere is it taught or even suggested in Peyman *et al.* that oligonucleotides have antiviral activity against multiple viruses acting by a sequence independent mode of action. Moreover, Peyman *et al.* only enabled four antisense oligonucleotides against HSV-1 in cell culture (as disclosed in column 14, lines 14-19 in Peyman). Peyman *et al.* only teaches how to stabilize and improve cell penetration by capping antisense oligonucleotides (with the addition of a cap of guanine at their extremities). Peyman *et al.* teaches in column 6, lines 8-9, that the effective oligonucleotides are understood to mean antisense oligonucleotides. By definition, an "antisense" is a molecule that interacts with complementary strands

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of nucleic acids, modifying the expression of genes. Consequently, a person skilled in the art would recognize that an antisense RNA or single-stranded antisense DNA is a molecule which is complementary to the nucleic acid sequence of a gene of interest. Thus, the mechanism of action of an antisense is sequence dependent since it must be complementary to a strand of a nucleic acid in order to interact and modify the expression of the gene of interest. In addition, such person skilled in the art would conclude that SEQ ID NOs: 1-34 disclosed by Peyman *et al.* represent sequences that are complementary to known genes, and thus represent antisense oligonucleotides. The Applicants previously submitted a Table identifying the gene targeted by these antisenses (see last response filed February 9, 2007). In column 6, lines 30-31; column 8, lines 29-30; column 10, lines 35-36; column 11, lines 4-5; and column 14, lines 14-19 of Peyman *et al.*, it is clearly stated that the oligonucleotides represented by SEQ ID NOs: 35-105 are examples of novel antisense effective against specific targets. All sequences listed in this patent are complementary to target sequences.

Consequently, SEQ ID NOs: 1-105 all represent antisense oligonucleotides which are complementary to a portion of the nucleic acid sequence of a specific gene. Thus, by its inherent properties, as well as by definition, an antisense will modify the expression of a gene by a sequence dependent mode of action. On the contrary, the Applicants submit that the present application teaches oligonucleotides having a sequence independent mode of action, as submitted hereinabove. This is reflected in the claims of Peyman *et al.* where an oligonucleotide having a nucleotide sequence complementary to a target sequence flanked by a Cap of guanines is claimed.

In addition, Peyman *et al.* discloses (in columns 1 and 2, under the Summary section), oligonucleotides having antiviral activity because they are antisenses and which have a Cap of guanine(s) at its 5' and/or 3' extremity to stabilize and improve cell penetration. To the contrary, the oligonucleotides disclosed in the present invention do not require being antisenses, nor do they need to have a Cap of guanines in order to have antiviral activity. Once again, a person skilled in the art would recognize that Peyman *et al.* teach antisense oligonucleotides wherein stabilization depends on the presence of a Cap of guanines and the antiviral activity depends on the sequence of the antisense oligonucleotide. Thus, the stabilization of the antisenses disclosed in Peyman is dependent on the presence of a secondary structure since, as stated in Peyman *et al.* (see column 1, lines 55-57), oligonucleotides which contain short segments of G residues are able to form intramolecular structures called G-quartets. Thus, not only is the antiviral activity dependent on the sequence, but the stabilization of the antisenses disclosed in Peyman is sequence dependent (in order to form the G-quartet structure). In view of the arguments presented hereinabove, it is believed that the claims now

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on file are novel in view of the teaching of Peyman *et al.*, and thus the Applicants respectfully submit that the 35 U.S.C. §102(e) rejection over Peyman *et al.* is improper, and requests that it be withdrawn.

Double Patenting

The Examiner maintained her rejection of claims 28 and 29 on the ground of nonstatutory double-patenting over copending Application Nos. 10/661,088 and 10/661,415.

In this matter, the Applicants submit that this rejection should now be moot in light of the Terminal Disclaimer under 37 C.F.R. §1.321 which was filed May 14, 2007.

In view of the foregoing, Applicants respectfully request that the double-patenting rejections be withdrawn.

It is submitted, therefore, that the claims are in condition for allowance, and prompt and favorable action in the form of a Notice of Allowance is earnestly solicited.

Respectfully submitted,

Date: May 15, 2007 By: _____

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